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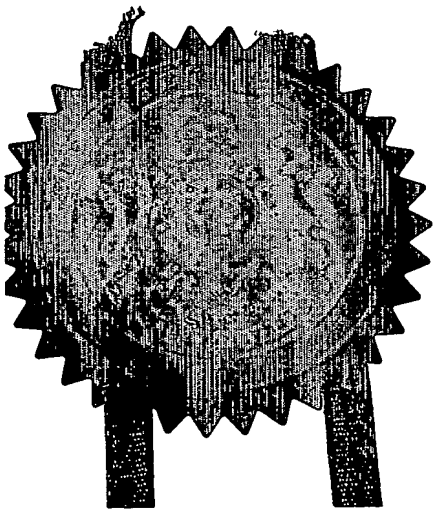

Signed R. Mahoney

Dated 3 July 2003

Patents Form 1/77

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1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your Reference — **AP/PI4862**

2. [illegible] — 0215392.2

- 3 JUL 2002 04JUL02 E730749-1 D01030
P01/7700 0.00-0215392.2

3. [illegible] of — **GLAXO GROUP LIMITED**
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

each applicant *(underline all surnames)*

Patents ADP number *(if you know it)* 07358700 2

If the applicant is a corporate body, give the country/state of its corporation — **GB**

4 Title of the invention — **CHEMICAL COMPOUNDS**

5 Name of your agent *(if you know one)* — **PETER I DOLTON**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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TW8 9GS, GB

Patents ADP number *(if you know it)* 8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

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Continuation sheets of this form	-
Description	27
Claim(s)	3
Abstract	2
Drawing(s)	-

RM.

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

P. I. Dolton

Signature PETER I DOLTON. 3 July 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY

020 8047 4420

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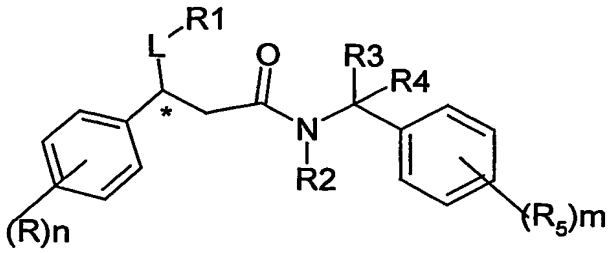
Chemical Compounds

The present invention relates to heterocyclic derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The present invention thus provides compounds of formula (I)



(I)

wherein

R represents halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl or trifluoromethoxy;

R_1 represents a 5 or 6 membered heteroaryl group, in which the 5-membered heteroaryl group contains at least one heteroatom selected from oxygen, sulphur or nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms, or R_1 represents a 4, 5 or 6 membered heterocyclic group, wherein saids 5 or 6 membered heteroaryl or the 4, 5 or 6 membered heterocyclic group may optionally be substituted by one to four substituents, which may be the same or different, selected from $(CH_2)_pR_6$, wherein p is zero or an integer from 1 to 4 and R_6 is selected from:

- halogen,
- C_{1-4}alkoxy,
- C_{1-4}alkyl,
- C_{3-7}cycloalkyl,
- hydroxy,
- cyano,
- nitro,
- trifluoromethyl,
- carboxy,
- $NH(C_{1-4}$ alkyl),
- $N(C_{1-4}$ alkyl$)_2$
- $NH(C_{3-7}$ cycloalkyl),
- $N(C_{1-4}$ alkyl$)(C_{3-7}$ cycloalkyl);

provided that saids 5 or 6 membered heteroaryl or 4, 5 or 6 membered heterocyclic are linked to the carbon atom shown as * via a carbon atom;

R_2 represents hydrogen, or C_{1-4} alkyl ;

R_3 and R_4 independently represent hydrogen, C_{1-4} alkyl or R_3 together with R_4 represents C_{3-7} cycloalkyl;

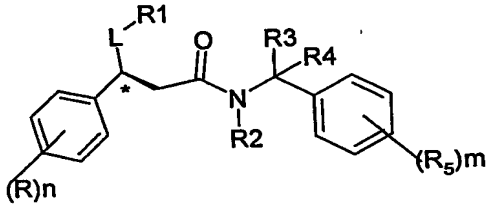
R_5 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;
L is a single or a double bond;
n is an integer from 1 to 3;
m is zero or an integer from 1 to 3;
and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, trifluoroacetates, acetates, citrates, succinates, tartrates,malates, lactates, fumarates and maleates.

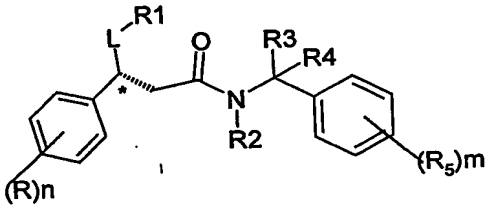
The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts and their pharmaceutically acceptable solvates.

It will be appreciated by those skilled in the art that the compounds of formula (I) wherein L is a single bond, contain at least one chiral centre (namely the carbon atom shown as * in formula (I)) and may be represented by formula (1a) and (1b).



(1a)



(1b)

The wedge bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.
The configuration shown for the chiral carbon indicated as * in formula (1a) is β and in formula(1b) is α.

Further asymmetric carbon atoms are possible in the compounds of formula (I) when R_3 and R_4 are not the same group.

It is to be understood that all stereoisomeric forms including all enantiomers and mixtures thereof are encompassed within the scope of the present invention and the reference to compound of formula (I) include all stereisomeric forms unless otherwise stated.

The term C_{1-4} alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include

methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, 1 methylethyl or 2-methyl propyl.

The term halogen refers to fluorine, chlorine, bromine or iodine.

The term C_{3-7} cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

When R_1 is a 5 or 6 membered heteroaryl group according to the invention this includes furanyl, thiophenyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,3-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,4 oxadiazolyl, 1,2,5-triazinyl or 1,3,5-triazinyl and the like.

The term 4, 5 or 6 membered heterocyclic group refers to 4, 5 or 6 ring member, containing at least one heteroatom selected from oxygen, sulphur or nitrogen, which may be saturated or unsaturated. Examples of such groups include azetidinyl, piperidyl, 2-oxodihydrofuranyl, piperazinyl, morpholinyl, pyrazolidinyl, 1,2 dihydro-3H-pyrazolyl, imidazolidinyl or pyrrolidinyl and the like.

The term C_{1-4} alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

R is preferably halogen (e.g. fluorine) and/or a C_{1-4} alkyl (e.g. methyl) group and n is preferably an integer from 1 to 2.

R_1 is preferably piperidine or pyrrolidine.

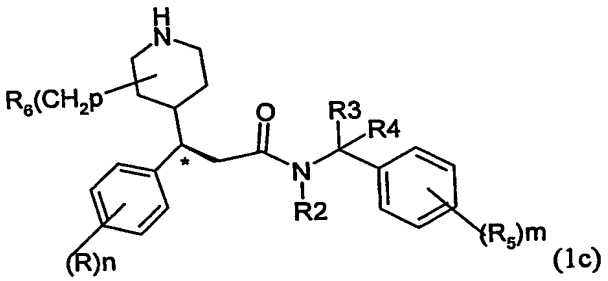
R_2 is preferably hydrogen or methyl.

R_3 is preferably hydrogen or methyl.

R_4 is preferably hydrogen, methyl or together with R_3 is cyclopropyl.

R_5 is preferably trifluoromethyl, methyl, chlorine or fluorine atom and q is preferably an integer from 1 to 2.

Preferred compounds of the invention are those of formula (1c)



(1c)

Particularly preferred compounds according to the invention are:
N-(3,5-Bis-trifluoromethyl-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide;
N-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide;
N-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide;
N-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-[1-(2-methoxyethyl)-piperidin-4-yl]-propionamide;
N-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide;
and enantiomers, diastereiosomers, pharmaceutically acceptable salts(e.g hydrochloride) and solvates thereof.

The compounds of the invention are antagonists of tachykinin receptors, including substance P and other neurokinins, both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

Tachykinins are a family of peptides that share a common carboxyl-terminal sequence (Phe-X-Gly-Leu-Met-NH2). They are actively involved in the physiology of both lower and advanced lifeforms. In mammalian lifeforms the main tachykinins are subtance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB) which act as neurotransmitters and neuromodulators. Mammalian tachykinins may contribute to the pathophysiology of a number of human diseases.
Three types of tachykinins receptors have been identified, namely NK1(SP-preferring), NK2 (NKA-preferring) and NK3 (NKB-preferring) which are widely distributed throughout the central nervous (CNS) and peripheral nervous system.

Particularly the compounds of the invention are antagonists of the NK1 receptor.

The compounds of the present invention also have activity as selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) and are thus of use in the treatment of conditions mediated by selective inhibition of the serotonin reuptake transporter protein.

Thus the compounds of the present invention combine dual activity as tachykinin antagonists, including substance P and other neurokinins, and as SSRIs. In particular, the compounds of the invention combine dual activity as NK1 receptor antagonists and as SSRIs.

NK_1-receptor binding affinity has been determined in vitro by measuring the compounds' ability to displace [3H] - substance P (SP) from recombinant human NK_1 receptors expressed in Chinese Hamster Ovary (CHO) cell membranes.

CHO cell membranes were prepared by using a modification of the method described by Beattie D.T. et al. (Br. J. Pharmacol, 116:3149-3157, 1995). Briefly, ligand binding was performed in 0.2 ml of 50 mM HEPES, pH 7.4, containing 3 mM $MnCl_2$, 0.02% BSA, 0.5 nM [^{3}H]-Substance P (30÷56 Ci/mmol, Amersham), a final membrane concentration of 20÷30 µg of protein/ml, and the test compounds. The incubation proceeded at room temperature for 40 min and stopped by filtration. Non-specific binding was determined using excess of Substance P (1 µM) and represents about 6÷10% of the total binding.

Compounds of the invention were further characterised in a functional assay for the determination of their effect to inhibit the intracellular calcium increase induced by SP in Human-NK_1-CHO cells using FLIPR technology. Briefly, after 30min incubation with the cytoplasmic calcium indicator Fluo-4 AM (2µM), cells were washed and incubated in the absence or presence of three different concentrations of antagonist for 60min, at 37°C in Hank's balanced salts with 20mM Hepes, and then non-cumulative concentration-response curves of SP (2pM-300nM) was performed. The potency of the antagonist (pK_B value) was calculated from Schild's analysis.

The action of the compounds of the invention at the NK_1 receptor and/or serotonin transporter may be determined by using conventional animal models. Thus the ability to bind at the NK_1 receptor and/or serotonin transporter was determined using the guinea pig pup isolation calls model as described by Pettijohn, Psychol. Rep., 1979 and Rupniak et al., Neuropharmacology, 2000.

Human Serotonin Transporter (hSERT) binding affinity has been determined in vitro by the compounds' ability to displace [^{3}H]- Imipramine from human serotonin transporter expressed in Human Embryonic Kidney HEK293 cell membranes (Receptor Biology Inc.). For the binding reaction, 4 nM of [^{3}H]- Imipramine (703 GBq/mmol, Amersham) were incubated with 0.02 mg/ml of cell membrane and the compound to be tested at different concentrations (7 concentration points) in 50 mM Tris HCl, pH 7.5, 120 mM of NaCl and 5 mM KCl. The reaction was performed for 60 min at 4°C and was terminated by through GF/B Unifilter (pre-soaked in 0.5 % PEI) using a Cell Harvester (Packard). Scintillation fluid was added to each filtered spot and radioactivity was determined using a scintillation counter (TopCount (Packard)). Non-specific binding was determined using Imipramine (100µM) and represents about 5% of the total binding.

For the preferred compounds of the invention Human Serotonin Transporter binding affinity has been also determined in vitro by the compounds ability to displace [3H] paroxetine.

Competition experiments were conducted with duplicate determination for each point.

Msat601 software package was used to elaborate the competition binding data.

IC_{50} values were converted to K_i values using Cheng-Prusoff equation.

The inhibitory activity of the compounds at the rat serotonin transporter has been determined in vitro using rSERT-LLCPK cells (LLCPK cells tranfected with the rat SERT). The cells have been plated onto 96-well plates (60000 cells/well). After 24 hr, cells have been washed in uptake buffer (Hank's balanced salt solution + 20 mM Hepes) and pre-incubated for 10 min at RT with 50 µl of buffer containing the test compounds. 50 µl of 50 nM [3H] Serotonin (5HT) solution (final concentration: 25 nM [3H] 5HT) have been added and plates have been incubated for 7 min at RT, during which cells take up radiolabelled 5HT. Aspirating the solution and rapidly washing the cells with cold buffer has terminated the uptake.
The amount of radioactive 5HT incorporated in the cells has been then measured by adding the scintillation cocktail directly onto the cells and reading the plate in the Top Count. The data have been digitally processed to obtain the pIC50 values of the antagonists. The pKi values have been calculated using the Chen-Prusoff equation.

Compounds of the invention are useful in the treatment of CNS disorders and psychotic disorders, in particular in the treatment or prevention of depressive states and /or in the treatment of anxiety as defined in, but not restricted to, Diagnostic statistical of mental disorder (DSM) IV edition edit by American psychiatric association SM-IV and international classification Diseases 10 th revision (ICD10) .
Thus for example depressive states include Major Depressive Disorder (MDD), including bipolar depression, unipolar depression, single or recurrent major depressive episodes , recurrent brief depression, with or without psychotic features, catatonic features, melancholic features including anorexia, weight loss, atypical features, anxious depression, cyclothymic or postpartum onset.
Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.
The term anxiety includes anxiety disorders, such as panic disorders with or without agoraphobia, agoraphobia , phobias for example social phobias or agoraphobia, obsessive-compulsive disorder, stress disorders including post traumatic stress disorder generalised anxiety disorder , acute stress disorders and mixed anxiety-depression disorders.

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic

neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of the cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment or prevention of schizophrenic disorders including paranoid schizophrenia, disorganised schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, residual schizoprenia.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The

compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

The compounds of the invention are also useful in premenstrual dysphoric disorder (PMDD), in chronic fatigue syndrome and Multiple sclerosis.

Compounds of the invention have been found to exhibit anxiolytic and antidepressant activity in conventional tests. For example in Guinea pig pups separation-induced vocalisations (Molewijk et al., 1996).

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of serotonin reuptake.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the treatment of conditions

mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

In a further aspect there is provided the use of a compounds of formula(I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of depression and /or anxiety.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention is provided a method for the treatment of a mammal, including man, in particular in the treatment of depression and /or anxiety which method comprises administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before

use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

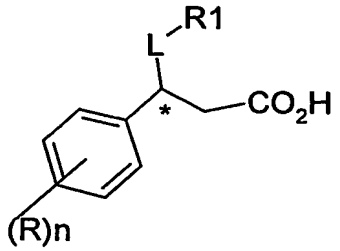
For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

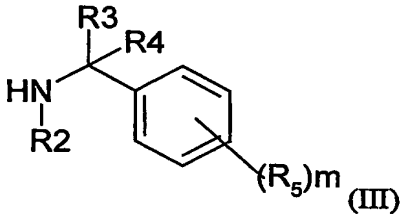
Thus for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 300 mg e.g. 1 to 100 mg.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1 R_2, R_3, R_4, R_5, R_6, L, m and n, have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (I) may be prepared by reaction of of an activated derivative of the carboxylic acid (II), wherein R_1 has the meaning previously defined or is nitrogen protecting group thereof, with amine (III)



(II)



(III)

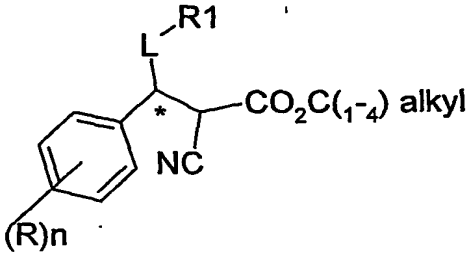
wherein R_2 is C_{1-4} alkyl or nitrogen protecting group, followed where necessary by removal of any nitrogen protecting group.

Suitable activated derivatives of the carboxyl group include the acyl halide, mixed anhydride, activated ester such as thioester or the derivative formed between the carboxylic acid group and a coupling agent such as that used in peptide chemistry, for example carbonyl diimidazole or dicyclohexylcarbodiimide.

The reaction is preferably carried out in an aprotic solvent such as hydrocarbon, halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran.

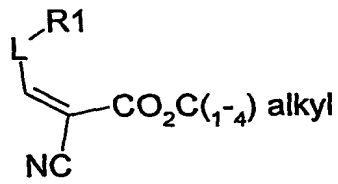
The activated derivatives of the carboxylic acid (II) may be prepared by conventional means. A particular suitable activated derivative for use in this reaction is O-(Benzotriazol-1-yl) – N,N,N',N'-tetramethyluronium tetrafluoroborate.

Compounds of formula (II), may be prepared by reaction of a cyano derivatives (IV) with a acid such as for example concentrated sulfuric acid. The reaction is conveniently carried out in a solvent such as acetic acid and heating the reaction mixture up to 150° .

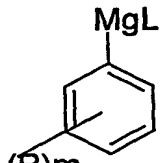


(IV)

Compounds of formula (IV) may be prepared by reaction of a compound of formula (V) with a compound of formula (VI) , wherein L is a halogen group (i.e bromine).



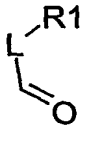
(V)



(VI)

The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon (i.e toluene) and at a temperature within the range 0-25°C.

Compounds of formula (V) may be prepared by reaction of a compounds of formula (VII) with a cyano derivative (VIII).



(VII)

$CNCHCO_2C(_{1}\text{-}_{4})alkyl$ (VIII)

Compounds of formulae (VI) (VII) and (VIII) may be prepared with analogous method to those used for known compounds. Thus compounds of formula (VI) may be prepared according to the procedure described by Jones LA et al., J. Organomet. Chem. (1985), 284 (2), 159-169.
Compounds of formula(VII) or (VIII) are known compounds or may be prepared according to the procedure used for known compounds.

Examples of suitable nitrogen protecting groups include alkoxycarbonyl e.g. t-butoxycarbonyl, benzyloxycarbonyl, arylsulphonyl e.g. phenysulphonyl or 2-trimethylsilylethoxymethyl.

Protection and deprotection may be effected using conventional techniques such as those described in "Protective Groups in Organic Synthesis 2nd Ed." by T.W. Greene and P. G. M. Wuts (John Wiley and Sons, 1991) and as described in the examples hereinafter.

Where it is desired to isolate a compound of formula (I) as a salt, for example a pharmaceutically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether, *tert*-butylmethyl ether or tetrahydrofuran).

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Buchi m.p. apparatus and are uncorrected. R.T. or r.t. refer to room temperature.
Infrared spectra (IR) were measures in chloroform or nujol solutions on a FT-IR instrument. Proton Magnetic Resonance (NMR) spectra were recorded on Varian instruments at 400 or 500 MHz, chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, double; t, triple; q, quartet; m, multiplet; b, broad. Mass spectra (MS) were taken on a VG Quattro mass spectrometer. Optical rotations were determined at 20°C with a Jasco DIP360 instrument (l=10 cm, cell volume = 1 mL, λ = 589 nm). Flash silica gel chromatography was carried out over silica gel 230-400 mesh supplied by Merck AG Darmstadt, Germany. T.l.c. refers to thin layer chromatography on 0.25 mm silica gel plates (60F-254 Merck) and visualized with UV light. Solutions were dried over anhydrous sodium sulphate.
Methylene chloride was redistilled over calcium hydride and tetrahydrofuran was redistilled over sodium.
The following abbreviation are used in the text: AcOEt = ethyl acetate, CH = cyclohexane, DCM = methylene chloride, DIPEA = N,N-diisopropylethylamine, DMF = N,N'-dimethylformamide, Et2O = diethyl ether, EtOH = ethanol, MeOH = methanol TEA = triethylamine, THF = tetrahydrofuran.
Enantiomer 1, enantiomer 2, diastereoisomer 1 , diastereoisomer 2, diastereoisomer 3 or diastereoisomer 4 refer to a single enantiomer or a single diasteroisomer respectively, whose absolute stereochemistry was not characterised.
Diastereoisomer A or diastereoisomer B refer to mixture of two diastereoisomers whose absolute stereochemistry was not characterised .

Intermediate 1

Piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester

A solution of di-*tert*-butyl-dicarbonate (7.07 mg) in anhydrous DCM (20 mL) was added to a solution of ethyl isonipecotate (5 mL) in anhydrous DCM (40 mL) previously cooled to 0°C under a Nitrogen atmosphere. The solution was stirred at r.t. overnight, then it was washed with 1N hydrochloric acid solution and brine. The organic phase was dried and concentrated *in vacuo* to give the title compound (8 g) as a pale yellow oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.67.
NMR ($CDCl_3$): δ (ppm) 4.11 (q, 2H); 3.96 (m, 2H); 2.8 (m, 2H); 2.38 (m, 1H); 1.85 (m, 2H); 1.6 (m, 2H); 1.42 (s, 9H); 1.25 (t, 3H).

Intermediate 2
Hydroxymethylpiperidine-1-carboxylic acid *tert*-butyl ester

Lithium aluminium hydride (1M solution in THF –17.8 mL) was added to a solution of intermediate 1 (8.0 g) in anhydrous THF (80 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 20 minutes, then it was treated with water (0.7 mL), 1M sodium hydroxide solution (0.7 mL) and water (2 mL). The inorganic salts were filtered off and the organic layer was concentrated *in vacuo* to give the title compound (7.0 g) as a yellow oil.
T.l.c.: CH/AcOEt 1:1, Rf=0.25 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 4.1 (m, 2H); 3.71 (m, 1H); 3.45 (m, 2H); 2.67 (m, 2H); 1.83 (m, 1H); 1.65 (m, 2H); 1.44 (s, 9H); 1.15 (m, 2H).

Intermediate 3
4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester
Method A

2,2,6,6-Tetramethylpiperidin-1-yl-oxy (free radical, TEMPO – 0.486 g) and iodobenzene diacetate (11.05 g) were added to a solution of intermediate 2 (7.0 g) in anhydrous DCM (40 mL). The mixture was stirred at r.t. overnight, then it was washed with a 20% sodium thiosulphate solution (50 mL) and brine.
The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (4.76 g) as a pale yellow foam.

Method B
Diisobutylaluminium hydride (1M in toluene – 8.6 mL) was dropped into a solution of intermediate 1 (1 g) in anhydrous toluene (13 mL) previously cooled to -78°C under a Nitrogen atmosphere over 30 minutes. The solution was stirred at -78°C for 2 hours, then it was quenched with a 10% sodium hydroxide solution (16 mL) at -78°C. The mixture was allowed to warm to r.t. and the layers were separated. The organic layer was washed with a 10% sodium hydroxide solution and brine, dried and concentrated *in vacuo* to give the title compound (0.7 g) as yellow foam.
T.l.c.: CH/AcOEt 7:3, Rf=0.35 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 9.63 (s, 1H); 3.98 (m, 2H); 2.89 (m, 2H); 2.35 (m, 1H); 1.85 (m, 2H); 1.57 (m, 2H).

Intermediate 4
4-(2-Cyano-2-ethoxycarbonyl-vinyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate 3 (4.5 g), ethyl cyanoacetate (2.47 mL), ammonium acetate (0.813 g) and acetic acid (1.27 mL) in anhydrous toluene (90 mL) was heated to 80°C for 3 hours, then it was allowed to cool to r..t. and washed with water, 1N sodium hydroxide solution and brine. The organic phase was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (from CH to CH/AcOEt 8:2) to give the title compound (5.5 g) as a white solid.

T.l.c.: CH/AcOEt 7:3, Rf=0.45 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 7.6 (d, 1H); 4.24 (q, 2H); 3.96 (bd, 2H); 2.8-2.71 (m, 3H); 1.61 (bd, 2H); 1.47-1.38 (bd, 2H); 1.39 (s, 9H); 1.25 (t, 3H).

MS (ES/+): m/z=309 $[M+H]^+$.

Intermediate 5

4-[2-Cyano-2-ethoxycarbonyl-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of 4-fluorophenyl magnesium bromide (2M in Et2O – 12.16 mL) in anhydrous Et2O (5 mL) was dropped into a solution of intermediate 4 (2.5 g) in anhydrous Et2O (20 mL) previously heated to reflux under a Nitrogen atmosphere. The mixture was diluted with further Et2O (10 mL) and heated to reflux for 30 minutes. The mixture was allowed to warm to r.t. and treated with 3N sulfuric acid solution (15 mL). The mixture was stirred at r.t. for 30 minutes, then AcOEt was added and the layers were separated. The aqueous layer was extracted with further AcOEt. The combined organic extracts were washed with a saturated sodium hydrogen carbonate and brine, then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (from CH to CH/AcOEt 8:2) to give the title compound (2.47 g – diastereoisomeric mixture) as a white foam.

T.l.c.: CH/AcOEt 7:3, Rf=0.38 (detection with ninhydrine).

NMR (d_6-DMSO - 80°C): δ (ppm) 7.32 (dd, 2H); 7.15 (t, 2H); 4.65 (d, 1H); 4.0 (q; 3H); 3.83 (m, 1H); 3.1 (dd, 1H); 2.76 (m, 1H); 2.63 (m, 1H); 1.95 (m, 1H); 1.87 (m, 1H); 1.38 (s, 9H); 1.2 (m, 1H); 1.14 (m, 1H); 0.92 (m, 1H).

MS (ES/+): m/z=405 $[M+H]^+$.

Intermediate 6

4-[2-Carboxy-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester

Method A

A mixture of intermediate 5 (2.4 g) in acetic acid (30 mL), conc sulfuric acid (8 mL) and water (9 mL) was heated to 140°C for 2.5 hours. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (300 mL). Then, di-*tert*-butyl-dicarbonate (1.35 g) was added and the resulting mixture was stirred at r.t. overnight. It was cooled to 0°C and treated with 3M hydrochloric acid solution until pH=6-7 and then extracted many times with AcOEt. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 1:1 to 2:8) to give the title compound (0.12 g) as a pale yellow foam.

Method B

A 3M potassium hydroxide solution (1.5 mL) was added to a solution of intermediate **9** (90 mg) in ethanol (2 mL). The mixture was heated in microwave (300W, P=300p.s.i.) at 150°C for 40 minutes. The solution was allowed to cool to r.t., acidified to pH=5 with a buffer solution pH3 (citrate-hydrochloric acid buffer solution purchase from Fluka) and extracted with AcOEt. The organic extract was dried and concentrated *in vacuo* to give the title compound (58 mg) as a white foam.

Method C

A solution of lithium hydroxide monohydrate (1.78 g) in water (27 mL) was added to a solution of intermediate **12** (3.1 g) in MeOH (100 mL). The mixture was heated to 80°C for 1 hour, then it was allowed to cool to r.t., diluted with water and concentrated to half volume. The residue was acidified with 3M hydrochloric acid solution and extracted with AcOEt. The organic layer was dried and concentrated *in vacuo* to give the title compound (2.7 g) as a white foam.

T.l.c.: CH/AcOEt 1:1, Rf=0.2 (detection with ninhydrine).

IR (nujol, cm^{-1}): 3200 (COOH), 1732 and 1690 (C=O).

NMR (d_6-DMSO): δ (ppm) 11.94 (bs, 1H); 7.2 (dd, 2H); 7.08 (dd, 2H); 3.95-2.6 (2m, 4H); 2.83-2.72 (m, 2H); 2.5 (m, 1H); 1.59 (m, 1H); 1.34 (s, 9H); 1.72-0.94 (m, 2H); 1.22-0.82 (m, 2H).

Intermediate 7

4-[2-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl)]-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester DIPEA (0.116 mL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (0.071 g) were added to a solution of intermediate **6** (0.06 g) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 20 minutes, (3,5-bis-trifluoromethyl-benzyl)-methylamine hydrochloride (0.1 g) was added. The mixture was stirred at r.t. for 4 hours, then it was diluted with AcOEt and washed with a 5% sodium hydrogen carbonate solution and brine. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (0.062 g) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.35.

IR (nujol, cm^{-1}): 1684 and 1645 (C=O).

NMR (d_6-DMSO): δ (ppm) 7.95 (s, 1H); 7.7 (s, 2H); 7.2 (dd, 2H); 7.0 (dd, 2H); 4.54 (q, 2H); 3.94-3.93 (2d, 2H); 3.3 (m, 1H); 3.01-2.98 (m, 1H); 2.96 (s, 3H); 2.81-2.75 (m, 2H); 1.74-1.58 (m, 2H); 1.34 (s, 9H); 1.27-1.18 (m, 2H); 0.99-0.76 (2q, 2H).

MS (ES/+): m/z=591 $[M+H]^+$.

Intermediate 8

4-[2-[(3,5-Dichloro-benzyl)-methyl-carbamoyl)]-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (0.116 mL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (0.071 g) were added to a solution of intermediate **6** (0.06 g) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 20 minutes, (3,5-dichloro-

benzyl)-methylamine hydrochloride (0.077 g) was added. The mixture was stirred at r.t. for 4 hours, then it was diluted with AcOEt and washed with a 5% sodium hydrogen carbonate solution and brine. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (0.048 g) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.31.

IR (nujol, cm^{-1}): 1688 and 1646 (C=O).

NMR (d_6-DMSO): δ (ppm) 7.43 (s, 1H); 7.22 (dd, 2H); 7.05 (dd, 2H); 6.98 (s, 2H); 4.37 (q, 2H); 3.9 (2d, 2H); 3.0-2.71 (m, 4H); 2.9 (s, 3H); 1.77-1.59 (m, 2H); 1.34 (s, 9H); 1.345-1.18 (m, 2H); 1.02-0.79 (2q, 2H).

MS (ES/+): m/z=523 $[M+H]^+$.

Intermediate 9

4-[2-Cyano-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate 5 (0.35 g), sodium chloride (17.5 mg) and water (35 μL) in dimethylsulfoxide (3 mL) was heated to 160°C for 2 hours. The mixture was allowed to cool to r.t., diluted with water and extracted with AcOEt. The organic layer was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (from CH to CH/AcOEt 7:3) to give the title compound (0.27 g) as a yellow oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.61 (detection with ninhydrine).

IR (nujol, cm^{-1}): 2245 (C≡N), 1681 (C=O).

NMR (d_6-DMSO): δ (ppm) 7.31 (dd, 2H); 7.16 (dd, 2H); 3.95-2.6 (2m, 4H); 2.9-2.8 (m, 2H); 2.7 (m, 1H); 1.7 (m, 1H); 1.35 (s, 9H); 1.74-0.99 (m, 2H).

MS (ES/+): m/z=333 $[M+H]^+$.

Intermediate 10

4-(4-Fluoro-benzoyl)-piperidine-1-carboxylic acid *tert*-butyl ester A solution of intermediate 3 (126.6 mg) in anhydrous Et2O (2 mL) was dropped into a solution of 4-fluorophenyl magnesium bromide (2M in Et2O – 1 mL) in anhydrous Et2O (0.5 mL) previously cooled to 0°C under a Nitrogen atmosphere. At the end of the addition the mixture was allowed to warm to r.t. and stirred at 23°C for 30 minutes. The mixture was quenched with a saturated ammonium chloride solution (2 mL). The aqueous layer was further extracted with AcOEt. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to give 4-[(4-fluoro-phenyl)hydroxy-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester (292.3 mg- T.l.c.: DCM/AcOEt 9:1, Rf=0.4).

This material was dissolved in anhydrous DCM (4 mL) and treated portion-wise with Dess Martin periodinane (254.5 mg) under a Nitrogen atmosphere. The brown solution was stirred at r.t. for 3 hours, then further Dess Martin periodinane (127.2 mg) was added. The solution was diluted with Et2O (16 mL) and poured into a saturated sodium hydrogen solution (16 mL) containing sodium thiosulphate (392 mg). The mixture was stirred for 10 minutes, then the phases were separated. The organic layer was washed with a saturated sodium hydrogen carbonate solution. The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (58 mg) as a yellow solid.

T.l.c.: DCM/AcOEt 9:1, Rf=0.82 (detection with ninhydrine).
IR (nujol, cm^{-1}): 1685 and 1675 (C=O).
NMR (d_6-DMSO): δ (ppm) 8.07 (t, 2H); 7.35 (t, 2H); 3.96 (d, 2H); 3.62 (t, 1H); 2.9 (bs, 2H); 1.74-1.39 (m, 4H); 1.39 (s, 9H).
MS (ES/+): m/z=308 $[M+H]^+$, 330 $[M+Na]^+$.

Intermediate 11
E-4-[2-Ethoxycarbonyl-1-(4-fluoro-phenyl)-vinyl]-piperidine-1-carboxylic acid *tert*-butyl ester (11a) and
Z-4-[2-Ethoxycarbonyl-1-(4-fluoro-phenyl)-vinyl]-piperidine-1-carboxylic acid *tert*-butyl ester (11b)

Triethylphosphonoacetate (1.33 g) was added to a suspension of sodium hydride (60% suspension in mineral oil – 200 mg) in anhydrous THF (7.4 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and stirred at 23°C for 20 minutes. Then, a solution of intermediate **10** (58 mg) in anhydrous THF (7.4 mL) was added and the resulting solution was heated to reflux for 48 hours. The solution was allowed to cool to r.t., diluted with water and extracted with Et2O. The organic layer was washed with water and brine, dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 9:1) to give:
intermediate **11a** (181 mg) as yellow oil;
intermediate **11b** (267 mg) as yellow oil.

Intermediate 11a:
T.l.c.: CH/AcOEt 7:3, Rf=0.64 (detection with ninhydrine).
NMR (d_6-DMSO): δ (ppm): 7.2 (m, 4H); 5.67 (s, 1H); 4.13 (q, 2H); 3.76 (t, 1H); 3.97-2.7 (m, 4H); 1.34 (s, 9H); 1.22 (t, 3H).
MS (ES/+): m/z=378 $[M+H]^+$, 400 $[M+Na]^+$.

Intermediate 11b:
T.l.c.: CH/AcOEt 7:3, Rf= 0.53 (detection with ninhydrine).
NMR (d_6-DMSO): δ (ppm): 7.2 (m, 4H); 5.83 (d, 1H); 3.87 (q, 2H); 3.96-2.63 (m, 4H); 3.6 (m, 1H); 1.63-1.17 (m, 4H); 1.36 (s, 9H); 0.97 (t, 3H).
MS (ES/+): m/z=378 $[M+H]^+$, 400 $[M+Na]^+$.

Intermediate 12
4-[2-Methoxycarbonyl-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester

Magnesium turnings (20.3 mg) were added to a solution of intermediate **11a** and **11b** (63 mg) in anhydrous MeOH (1.7 mL) under a Nitrogen atmosphere with a low heating until hydrogen evolution is observed. Then, the reaction mixture was stirred at r.t. overnight, then water (2 mL) and a 10% acetic acid solution were added until dissolution of the magnesium salts. The mixture was made basic until pH=8.5 with 32% ammonium hydroxide solution and extracted with Et2O. The organic phase was washed with water and a saturated sodium hydrogen carbonate solution, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (37 mg) as a yellow oil.
IR (nujol, cm^{-1}): 1739 and 1694 (C=O).

NMR (d_6-DMSO): δ (ppm) 7.08 (t, 2H); 7.2 (dd, 2H); 3.93-3.84 (dd, 2H); 3.41 (s, 3H); 2.84-2.61 (q, 4H); 2.8 (m, 1H); 1.73-0.93 (m, 2H); 1.6 (m, 1H); 1.34 (s, 9H); 1.21-0.84 (m, 2H).
MS (ES/+): m/z=366 $[M+H]^+$.

Intermediate 13
4-[2-[1-(3,5-Dichloro-phenyl)-ethyl]-methyl-carbamoyl]-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester (13a –diastereoisomer A)and 4-[2-[1-(3,5-Dichloro-phenyl)-ethyl]-methyl-carbamoyl]-1-(4-fluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester (13b –diastereoisomer B)

DIPEA (595 µL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (0.563 g) were added to a solution of intermediate **6** (0.4 g) in anhydrous DMF (7 mL) under a Nitrogen atmosphere. After stirring for 30 minutes, intermediate **15** (0.256 g) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt and washed with a saturated ammonium chloride solution. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give:
intermediate **13a** (180 mg) as yellow oil
intermediate **13b** (180 mg) as yellow oil.
Intermediate **13a:**
T.l.c.: CH/AcOEt 1:1, Rf=0.37.
NMR (d_6-DMSO): δ (ppm) 7.48 (s, 1H); 7.15 (s, 2H); 7.21 (m, 2H); 7.09 (t, 2H); 5.58 (q, 1H); 4.0-3.8 (dd, 2H); 3.0-2.8 (dd, 2H); 3.0 (m, 1H); 2.8 (s, 3H); 2.6 (m, 1H); 1.8-0.8 (m, 4H); 1.4-1.2 (d, 3H); 1.34 (s, 9H).
Intermediate **13b:**
T.l.c.: CH/AcOEt 1:1, Rf=0.30.
MS (ES/+): m/z=559 $[M+Na]^+$.

Intermediate 14
3',5'-Dichloroacetophenone

A solution of methyl iodide (4 mL) in anhydrous Et2O (40 mL) was dropped into a suspension of magnesium (1.6 g) in anhydrous Et2O (16 mL) under a Nitrogen atmosphere. At the end of the dropping, benzene (120 mL) was added and the Et2O eliminated with a Nitrogen flux. Then, a solution of 3,5-dichlorobenzonitrile (4 g) in benzene (48 mL) was added and the mixture was heated to reflux for 3 hours. The solution was cooled to 0°C and a 6N hydrochloric acid solution was added and the mixture was stirred overnight at r.t.. Water and Et2O were added and the layers were separated. The organic phase was washed with a saturated sodium hydrogen carbonate solution and brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 95:5) to give the title compound (2.55 g) as an orange oil.
T.l.c.: CH/AcOEt 8:2, Rf=0.64.
NMR ($CDCl_3$): δ (ppm) 7.75 (s, 2H); 7.6 (s, 1H); 2.55 (s, 3H).

Intermediate 15
[1-(3,5-Dichloro-phenyl)-ethyl]-methylamine

Methylamine (2M solution in MeOH – 13 mL) was added to a solution of intermediate **14** (500 mg) in MeOH (26 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. for 18 hours, then it was cooled to 0°C and sodium borohydride (98 mg) was added. The mixture was stirred at 0°C for 2 hours, then it was quenched with water and extracted with DCM. The organic layer was dried and concentrated *in vacuo* to give the title compound (340 mg) as yellow oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.15.

NMR ($CDCl_3$): δ (ppm) 7.3 (m, 3H); 3.6 (q, 1H); 2.3 (s, 3H); 1.35 (d, 3H).

MS (ES/+): m/z=204 $[M+H]^+$.

Intermediate 16

1-Oxa-6-aza-spiro[2.5]octane-6-carboxylic acid *tert*-butyl ester

Sodium hydride (60% suspension in mineral oil – 3.6 g) was added to a solution of trimethylsulfoxonium iodide (19.8 g) in anhydrous DMSO (200 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. for 1 hour, then a solution of 1-(*tert*-butoxycarbonyl)-4-piperidone (15 g) in anhydrous DMSO (200 mL) was added. The mixture was heated to 60°C for 1.5 hours. The mixture was diluted with AcOEt (1 l) and washed with water and ice. The layers were separated. The aqueous layer was extracted with further AcOEt (500 mL). The combined organic extracts were washed with brine and dried. After concentration *in vacuo*, the crude was purified using a Biotage column (CH/AcOEt 8:2) to give the title compound (14.2 g).

T.l.c.: CH/AcOEt 7:3, Rf=0.61.

IR (nujol, cm^{-1}): 1699 (C=O).

NMR ($CDCl_3$): δ (ppm) 3.54 (m, 2H); 3.4 (m, 2H); 2.68 (s, 2H); 1.67 (m, 2H); 1.44 (s, 9H); 1.42 (m, 2H).

Intermediate 17

4-Fluoro-4-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

A 70% solution of hydrofluoric acid in pyridine (12 mL) was added drop-wise to a solution of intermediate **16** (10 g) in anhydrous DCM (200 mL) previously cooled to –40°C under a Nitrogen atmosphere. After 1.5 hours, further hydrofluoric acid in pyridine (6 mL) was added.

After stirring for further 15 minutes, a saturated sodium hydrogen carbonate solution was added. The layers were separated and the aqueous phase was extracted three times with further DCM. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (CH/AcOEt 6:4) to give the pure title compound (990 mg) and a fraction of title compound (6.01 g) impure of pyridine. Thus, this material was diluted with AcOEt and washed three times with a pH3 buffer solution and brine. The organic layer was dried and concentrated *in vacuo* to give a further amount of title compound (5.12 g).

T.l.c.: CH/AcOEt 1:1, Rf=0.35.

NMR (d_6-DMSO): δ (ppm) 4.99 (t, 1H); 3.79 (m, 2H); 3.43 (dd, 2H); 3.01 (bt, 2H); 1.8-1.4 (m, 4H); 1.43 (s, 9H).

Intermediate 18

4-Fluoro-4-formyl-piperidine-1-carboxylic acid *tert*-butyl ester

Dimethylsulfoxide (3.8 mL) was added to a solution of oxalyl choride (1.7 mL) in anhydrous DCM (126 mL) previously cooled to –78°C under a Nitrogen atmosphere. The solution was stirred at –78°C for 1 hour, then a solution of intermediate **17** (2.5 g) in anhydrous DCM (36 mL) was dropped over 1 hour. The mixture was stirred at –78°C for 30 minutes, then TEA (7.4 mL) was added. The mixture was allowed to warm to r.t. over 1.5 hours, then it was washed with water, 5% sodium hydrogen carbonate solution and brine. The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (1.7 g).

NMR (d_6-DMSO): δ (ppm) 9.64 (d, 1H); 3.89-3.78 (m, 4H); 1.82-1.59 (m, 4H); 1.39 (s, 9H).

MS (ES/+): m/z=232$[M+H]^+$.

Intermediate 19

4-(2-Cyano-2-ethoxycarbonyl-vinyl)-4-fluoro-piperidine-1-carboxylic acid *tert*-butyl ester

A round bottom flask equipped with a Dean stark apparatus was charged with intermediate **18** (1.4 g), ethyl cyanoacetate (0.71 mL), ammonium acetate (233.5 mg) and acetic acid (0.35 mL) in anhydrous toluene (30 mL) under a Nitrogen atmosphere. The mixture was heated to 95°C for 4 hours, then to 120°C for 30 minutes. The mixture was allowed to cool to r.t. and further ethyl cyanoacetate (0.2 mL) was added. The mixture was heated to 120°C for 1 hour, then left at 90°C overnight. The reaction mixture was allowed to cool to r.t... diluted with AcOEt and washed with water (20 mL), 0.5M sodium hydroxide solution (3 x 20 mL), water (20 mL) and brine (30 mL). The organic phase was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (1.33 g).

T.l.c.: CH/AcOEt 7:3, Rf=0.26 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 7.74 (d, 1H); 4.26 (q, 2H); 3.9 (bs, 2H); 2.98 (m, 2H); 1.99 (m, 2H); 1.78 (m, 2H); 1.4 (s, 9H); 1.26 (t, 3H).

MS (ES/+): m/z=327 $[M+H]^+$.

Intermediate 20

4-(2-Cyano-2-ethoxycarbonyl)-1-(4-fluoro-phenyl)-4-fluoro-piperidine-1-carboxylic acid *tert*-butyl ester

4-Fluorophenyl magnesium bromide (1M in THF – 4.6 mL) was dropped into a solution of intermediate **19** (500 mg) in anhydrous Et2O (20 mL) over 15 minutes under a Nitrogen atmosphere. The mixture was heated to reflux for 40 minutes. The mixture was allowed to warm to r.t. and treated with a saturated ammonium chloride solution (15 mL) and water (15 mL). The mixture was extracted with Et2O (3 x 30 mL). The combined organic extracts were washed with a saturated sodium hydrogen carbonate and brine, then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (520 mg) as a colourless oil.

T.l.c.: CH/AcOEt 7:3, Rf=0.26(detection with ninhydrine).
IR (nujol, cm^{-1}): 2247 (CN); 1747 and 1690 (C=O).
NMR (d_6-DMSO): δ (ppm) 7.46 (dd, 2H); 7.2 (dd, 2H); 4.92 (d, 1H); 4.02 (q, 2H); 3.87 (bm, 1H); 3.75 (bm, 1H); 3.64 (dd, 1H); 2.94 (bm, 1H); 2.8 (bm, 1H); 1.64 (td, 1H); 1.54 (m, 1H); 1.44 (m, 1H); 1.36 (s, 9H); 1.03 (t, 3H).
MS (ES/+): m/z=423 $[M+H]^+$.

Intermediate 21
4-(2-Cyano-1-(4-fluoro-phenyl)-ethyl]-4-fluoro-piperidine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate **20** (500 mg), sodium chloride (20 mg) and water (130 □L) in anhydrous dimethylsulfoxide (4 mL) was heated to 150°C for 1.5 hours. The mixture was allowed to cool to r.t., diluted with AcOEt (30 mL) and washed with water and brine. The organic layer was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (260 mg) as a colourless wax.
T.l.c.: CH/AcOEt 6:4, Rf=0.45(detection with ninhydrine).
MS (ES/+): m/z=295 $[M-tBu]^+$.

Intermediate 22
4-(2-Carboxy-1-(4-fluoro-phenyl)-ethyl]-4-fluoro-piperidine-1-carboxylic acid *tert*-butyl ester

A 3M potassium hydroxide solution (3 mL) was added to a solution of intermediate **21** (80 mg) in abs. EtOH (3 mL). The mixture was heated in microwave (300W, P=90p.s.i.) at 150°C for 10+10+10 minutes. The solution was allowed to cool to r.t., acidified to pH=5 with a pH3 buffer solution (citrate-hydrochloric acid buffer solution purchase from Fluka) and 2N hydrochloric acid solution and extracted with AcOEt (3 x 25 mL). The organic extract was dried and concentrated *in vacuo* to give the title compound (56 mg) as a white solid.
T.l.c.: AcOEt 100%, Rf=0.7 (detection with ninhydrine).
NMR (d_6-DMSO): δ (ppm) 12.05 (bs, 1H); 7.28 (m, 2H); 7.12 (m, 2H); 3.79 (m, 2H); 3.26 (m, 1H); 2.88 (dd, 1H); 2.8 (bm, 2H); 2.67 (dd, 1H); 1.8-1.4 (m, 4H).
MS (ES/+): m/z=370 $[M+H]^+$, 314 $[M-tBu]^+$.

Intermediate 23
4-[2-[(3,5-Dichloro-benzyl)-methyl-carbamoyl]-1-(4-fluoro-phenyl)-ethyl]-4-fluoro-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (80 μL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (65 mg) were added to a solution of intermediate **21** (56 mg) in anhydrous DMF (4 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-dichlorobenzyl-methylamine hydrochloride (40 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with water (5 mL) and extracted with AcOEt (20 mL). The aqueous layer was extracted with AcOEt (3 x 15 mL). The combined organic extracts were washed with brine, dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (65 mg) as a whitish foam.

T.l.c.: CH/AcOEt 4:6, Rf=0.5.
IR (nujol, cm^{-1}): 1688 and 1646 (C=O).
MS (ES/+): m/z=563 $[M+Na]^+$, 465 $[M-tBu-HF]^+$.

Example 1

***N*-(3,5-Bis-trifluoromethyl-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide**

TFA (0.8 mL) was added to a solution of intermediate 7 (0.06 g) in DCM (1 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 3 hours, then the solution was diluted with further DCM and washed with a saturated potassium carbonate solution and brine. The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (from AcOEt to AcOEt/MeOH 1:1 and finally to AcOEt/MeOH 4:6 containing 2% of conc. ammonium hydroxide solution) to give the title compound (0.043 g) as a pale yellow oil.
T.l.c.: AcOEt/MeOH 1:1 containing 2% of conc. NH4OH, Rf=0.1.
IR (film, cm^{-1}): 3320 (NH), 1646 (C=O).
NMR (d_6-DMSO): δ (ppm) 7.95 (s, 1H); 7.7 (s, 2H); 7.17 (s, 2H); 6.98 (dd, 2H); 4.54 (q, 2H); 2.94 (s, 3H); 2.92-2.71 (m, 5H); 2.4-2.24 (2td, 2H); 1.69-1.43 (m, 2H); 1.2 (db, 1H); 1.04-0.75 (2qd, 2H).
MS (ES/+): m/z=491 $[M+H]^+$.

Example 2

***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide**

TFA (0.73 mL) was added to a solution of intermediate 8 (0.048 g) in DCM (0.96 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 3 hours, then the solution was diluted with further DCM and washed with a saturated potassium carbonate solution and brine. The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (from AcOEt to AcOEt/MeOH 1:1 and finally to AcOEt/MeOH 4:6 containing 2% of conc. ammonium hydroxide solution) to give the title compound (0.031 g) as a pale yellow oil.
T.l.c.: AcOEt/MeOH 1:1 containing 2% of conc. NH4OH, Rf=0.08.
IR (film, cm^{-1}): 3320 (NH), 1646 (C=O).
NMR (d_6-DMSO): δ (ppm) 7.43 (t, 1H); 7.2 (dd, 2H); 7.04 (dd, 2H); 6.98 (s, 2H); 4.37 (q, 2H); 2.89 (s, 3H); 2.94-2.7 (m, 5H); 2.4-2.19 (2td, 2H); 1.74-1.15 (m, 3H); 1.04-0.77 (m, 2H).
MS (ES/+): m/z=423 $[M+H]^+$.

Example 3

***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide (3a) (enatiomer 1) and**

***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide (3b) (enantiomer 2)**

The compound of example 2 (10 mg) was separated into the enantiomers via HPLC (Column: Chiralcel OD 25cm x 4.6mm; mobile phase: n-hexane/EtOH 70:30; flux=1 mL/min; λ=225 nm). Thus, example 3a (3 mg) and example 3b (1.8 mg) were obtained.

Example 3a:
Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm, mobile phase n-hexane/EtOH 70:30, flux=1 mL/min, λ=225 nm, retention time 5.8 minutes. Ratio **3a/3b**=100:0.
Example 3b:
Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm, mobile phase n-hexane/EtOH 70:30, flux=1 mL/min, λ=225 nm, retention time 10.2 minutes. Ratio **3a/3b**=0:100.

Example 4
***N*-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide**
TFA (1.5 mL) was added to a solution of intermediate **13a** (0.17 g) in DCM (6 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then the solution was diluted with further DCM and washed with a saturated potassium carbonate solution. The organic extracts were dried and concentrated *in vacuo* to give the crude title compound (136 mg). A part of the residue (64 mg) was purified on SCX cartridge (ammonium hydroxide 0.25 M in MeOH) to give the title compound (60 mg) as a colourless oil.
NMR (d_6-DMSO): δ (ppm) 7.06 (t, 2H); 7.18 (m, 2H);7.15 (s, 2H); 7.48 (s, 1H); 5.58 (q, 1H); 2.91-2.8 (2m, 2H); 2.91-2.4 (2 m, 2H); 2.8-2.25 (t + m , 2H); 2.64 (s, 3H); 2.6 (m, 1H); 1.67-0.99 (q + d, 2H); 1.2 (s, 3H); 1.2-0.83 (2m, 2H).
MS (ES/+): m/z=437 $[M+H]^+$.

Example 5
***N*-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide**
TFA (1.5 mL) was added to a solution of intermediate **13b** (0.17 g) in DCM (6 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then the solution was diluted with further DCM and washed with a saturated potassium carbonate solution. The organic extracts were dried and concentrated *in vacuo* to give the crude title compound (136 mg). A part of the residue (64 mg) was purified on SCX cartridge (ammonium hydroxide 0.25 M in MeOH) to give the title compound (60 mg) as a colourless oil.
NMR (d_6-DMSO): δ (ppm) 7.42 (s, 1H); 7.03 (t, 2H); 7.2 (dd, 2H);6.85 (s, 2H); 5.6 (q, 1H); 3.0-2.8 (m, 4H); 2.61 (s, 3H); 2.6 (m, 1H); 1.71 (bd, 1H); 1.51-1.0 (2m, 2H); 1.32 (d, 3H); 1.16-0.84- (2m, 2H).
MS (ES/+): m/z=437 $[M+H]^+$.

Example 6
***N*-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide (6a) (diastereoisomer 1) and *N*-[1-(3,5-Dichloro-phenyl)-ethyl]--3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide (6b) (diastereoisomer 2)**

The compound of example 4 (35 mg) was separated into the enantiomers via HPLC (Column: Chiralpack AD 25cm x 4.6mm; mobile phase: n-hexane/EtOH 80:20; flux=7 mL/min; □□225 nm). Thus, example **6a** (16 mg) and example **6b** (14 mg) were obtained.

Example 6a:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm, mobile phase n-hexane/EtOH 80:20, flux=1 mL/min, λ=225 nm, retention time 8.9 minutes. Ratio **6a/6b**=100:0.

Example 6b:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm, mobile phase n-hexane/EtOH 80:20, flux=1 mL/min, λ=225 nm, retention time 10.7 minutes. Ratio **6a/6b**=0:100.

Example 7

***N*-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide (7a) (diastereoisomer 3) and *N*-[1-(3,5-Dichloro-phenyl)-ethyl]--3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide (7b) (diastereoisomer 4)**

The compound of example **5** (25mg) was separated into the enantiomers via HPLC (Column: Chiralcel OD 25cm x 4.6mm; mobile phase: n-hexane/EtOH 8:2; flux=1 mL/min; □□225 nm). Thus, example **7a** (9 mg) and example **7b** (9 mg) were obtained.

Example 7a:

Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm, mobile phase n-hexane/EtOH 8:2, flux=1 mL/min, λ=225 nm, retention time 6.7 minutes. Ratio **7a/7b**=100:0.

Example 7b:

Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm, mobile phase n-hexane/EtOH 8:2, flux=1 mL/min, λ=225 nm, retention time 10.1 minutes. Ratio **7a/7b**=0:100.

Example 8

***N*-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-[1-(2-methoxyethyl)-piperidin-4-yl]-propionamide (diastereoisomer A)**

A mixture of example 4 (72 mg), DIPEA (115 µL) and 2-bromoethyl methyl ether (19 µL) in acetonitrile (5 mL) was heated to reflux overnight. Water was added and the mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt and washed with a saturated ammonium chloride solution. The layers were separated. The organic layer was extracted with further AcOEt. The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (DCM/MeOH 9:1) to give the title compound (57 mg) as a colourless oil.

NMR (d_6-DMSO): δ (ppm) 7.48 (s, 1H); 7.2 (m, 2H); 7.15 (s, 2H); 7.06 (t, 2H); 5.58 (q, 1H); 3.35 (t, 2H); 3.18 (s, 3H); 2.94-2.86 (2m, 2H); 2.9-2.4 (2 m, 2H); 2.8-2.25 (t + m , 2H); 2.63 (s, 3H); 2.6 (m, 1H); 2.37 (dd, 2H); 1.85-1.12 (q + t, 2 H); 1.73-0.97 (2q, 2H); 1.2 (s, 3H);.

MS (ES/+): m/z=495 $[M+H]^+$.

Example 9

***N*-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-[1-(2-methoxyethyl)-piperidin-4-yl]-propionamide (diastereoisomer B)**

A mixture of example **5** (79 mg), DIPEA (126 µL) and 2-bromoethyl methyl ether (20 µL) in acetonitrile (5 mL) was heated to reflux overnight. Water was added and the mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt and washed with a saturated ammonium chloride solution. The layers were separated. The organic layer was extracted with further AcOEt. The combined organic extracts were dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (DCM/MeOH 95:5) to give the title compound (35 mg) as a colourless oil.
NMR (d_6-DMSO): δ (ppm) 7.42 (s, 1H); 7.15 (s, 2H); 7.04 (t, 2H); 6.85 (s, 2H); 5.6 (q, 1H); 3.37 (t, 2H); 3.19 (s, 3H); 3.0-2.8 (m , 6H); 2.61 (s, 3H); 2.41 (bs, 2H); 1.76 (d, 1H); 1.45-1.21 (2m, 2H); 1.32 (d, 3H); 1.27-0.99 (q, 2H); 1.21 (m, 1H).
MS (ES/+): m/z=495 $[M+H]^+$.

Example 10
***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide**

A solution of TFA (1 mL) in anhydrous DCM (3 mL) was added to a solution of intermediate **23** (64 mg) in anhydrous DCM (1 mL) previously cooled to –10°C under a Nitrogen atmosphere. The resulting solution was stirred at –10°C for 2 hours, then the solution was concentrated *in vacuo*. The residue was diluted with AcOEt/water and washed with a saturated potassium carbonate solution. The aqueous layer was extracted with further AcOEt (3 x 20 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (DCM/MeOH 8:2) to give the title compound (40 mg) as a white foam.
T.l.c.: DCM/MeOH 8:2, Rf=0.1.
NMR (d_6-DMSO): δ (ppm) 7.42 (t, 1H); 7.28 (dd, 2H); 7.07 (dd, 2H); 6.95 (d, 2H); 4.51 (d, 1H); 4.23 (d, 1H); 3.38 (m, 1H); 2.97 (dd, 1H); 2.94 (s, 3H); 2.86 (dd, 1H); 2.74 (m, 1H); 2.66 (m, 1H); 2.63 (m, 1H); 2.54 (m, 1H); 1.78 (m, 1H); 1.47 (m, 1H); 1.4 (m, 1H); 1.34 (m, 1H).

Example 11
***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide hydrochloride**

Hydrochloric acid (1 m in Et2O – 20 µL) was added to a solution of example **10** (7.8 mg) in anhydrous Et2O (1 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 15 minutes, then the liquid phase was removed. The residue was triturated with pentane (2 x 1 mL) and with pentane/Et2O 1:1 (1.5 mL) to give the title compound (5 mg) as a white solid.
MS (ES/+): m/z=441 $[M+H-HCl]^+$.

Example 12
***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide (12a - enantiomer 1) and**
***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide (12b – enantiomer 2)**

The compound of example **10** (32 mg) was separated into the enantiomers via HPLC (Column: Chiralcel OD 25cm x 20mm; mobile phase: n-hexane/EtOH 70:30; flux=6.4 mL/min; λ=225 nm). Thus, example **12a** (15 mg) and example **12b** (14 mg) were obtained.

Example 12a:

Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 80:20, flux=1 mL/min, λ=225 nm, retention time 8.1 minutes. Ratio **12a/12b**=100:0.

Example 12b:

Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 80:20, flux=1 mL/min, λ=225 nm, retention time 22.4 minutes. Ratio **12a/12b**=0:100.

Example 13

***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide hydrochloride**

Hydrochloric acid (1M in Et2O – 38 μL) was added to a solution of example **12a** (15 mg) in anhydrous Et2O (1.5 mL) previously cooled to –10°C under a Nitrogen atmosphere. The mixture was stirred at –10°C for 30 minutes, then it was concentrated *in vacuo*. The residue was triturated with pentane (2 x 1 mL) and pentane/Et2O 1:1 (1.5 mL) to give the title compound (11 mg) as white solid.

Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 80:20, flux=1 mL/min, λ=225 nm, retention time 7.96 minutes.

MS (ES/+): m/z=441 $[M+H-HCl]^+$.

Example 14

***N*-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide hydrochloride**

Hydrochloric acid (1M in Et2O - 35 μL) was added to a solution of example **12b** (14 mg) in anhydrous Et2O (1.5 mL) previously cooled to –10°C under a Nitrogen atmosphere. The mixture was stirred at –10°C for 30 minutes, then it was concentrated *in vacuo*. The residue was triturated with pentane (2 x 1 mL) and pentane/Et2O 1:1 (1.5 mL) to give the title compound (10 mg) as a white solid.

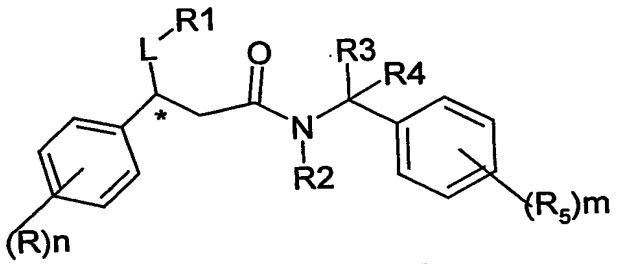
Chiral HPLC: Column Chiralcel OD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 80:20, flux=1 mL/min, λ=225 nm, retention time 22.2 minutes.

NMR (d_6-DMSO): δ (ppm) 8.39 (bm, 1H); 7.39 (s, 1H); 7.31 (dd, 2H); 7.08 (dd, 2H); 6.92 (s, 2H); 4.5 (d, 1H); 4.18 (d, 1H); 3.47 (m, 1H); 3.17 (m, 1H); 3.12 (m, 1H); 3.02 (dd, 1H); 2.92 (s, 3H); 2.89 (m, 1H); 2.85 (dd, 1H); 2.82 (m, 1H); 2.06 (m, 1H); 1.75 (m, 1H); 1.65 (m, 2H);

MS (ES/+): m/z=441 $[M+H-HCl]^+$.

Claims

1. A compound of formula (I)



(I)

wherein

R represents halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl or trifluoromethoxy;

R_1 represents a 5 or 6 membered heteroaryl group, in which the 5-membered heteroaryl group contains at least one heteroatom selected from oxygen, sulphur or nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms, or R_1 represents a 4, 5 or 6 membered heterocyclic group, wherein saids 5 or 6 membered heteroaryl or the 4, 5 or 6 membered heterocyclic group may optionally be substituted by one to four substituents, which may be the same or different, selected from $(CH_2)_pR_6$, wherein p is zero or an integer from 1 to 4 and R_6 is selected from:

halogen,
C_{1-4}alkoxy,
C_{1-4}alkyl,
C_{3-7}cycloalkyl,
hydroxy,
cyano,
nitro,
trifluoromethyl,
carboxy,
NH(C_{1-4} alkyl),
N (C_{1-4} alkyl)$_2$
NH(C_{3-7} cycloalkyl),
N(C_{1-4} alkyl)(C_{3-7} cycloalkyl);

provided that saids 5 or 6 membered heteroaryl or 4, 5 or 6 membered heterocyclic are linked to the carbon atom shown as * via a carbon atom;

R_2 represents hydrogen, or C_{1-4} alkyl ;

R_3 and R_4 independently represent hydrogen, C_{1-4} alkyl or R_3 together with R_4 represents C_{3-7} cycloalkyl;

R_5 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

L is a single or a double bond;

n is an integer from 1 to 3;

m is zero or an integer from 1 to 3;
and pharmaceutically acceptable salts and solvates thereof.

2. A compound selected from:
N-(3,5-dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;
N-(3,5-dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;
4-(4-fluorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(4-chlorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(4-fluorophenyl)-piperidine-4-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;
N-(3,5-Bis-trifluoromethyl)-benzyl-2-[(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide;
N-(3,5-Bis-trifluoromethyl-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide;
N-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide;
N-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-piperidin-4-yl-propionamide;
N-[1-(3,5-Dichloro-phenyl)-ethyl]-3-(4-fluoro-phenyl)-*N*-methyl-3-[1-(2-methoxyethyl)-piperidin-4-yl]-propionamide;
N-(3,5-Dichloro-benzyl)-3-(4-fluoro-phenyl)-3-(4-fluoro-piperidin-4-yl)-*N*-methyl-proprionamide;
and enantiomers, diastereiosomers, pharmaceutically acceptable salts(e.g. hydrochloride) and solvates thereof.

3. A compound as claimed in claim 1 or 2 for use in therapy.

4. The use of a compound as claimed in claim 1 or 2 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

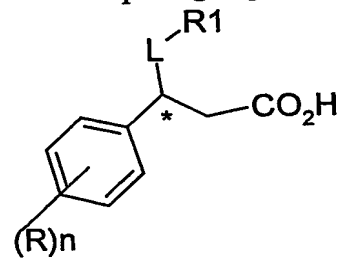
5. The use of a compound as claimed in claim 1 or 2 in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

6. A pharmaceutical composition comprising a compound as claimed in claim 1 or 2 in admixture with one or more pharmaceutically acceptable carriers or excipients.

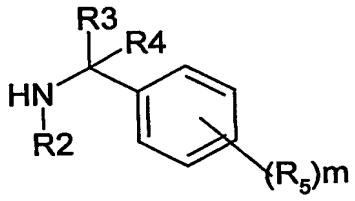
7. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein.

comprising administration of an effective amount of a compound of formula (I) as claimed in claim 1 or 2.

8. A process for the preparation of a compound as claimed in claim 1 or 2, which comprises reacting an activated derivative of the carboxylic acid of formula (II), wherein R_1 is a group as defined in claim 1 or a protecting group thereof, with amine (III)



(II)



(III)

followed where necessary or desired by one or more of the following steps

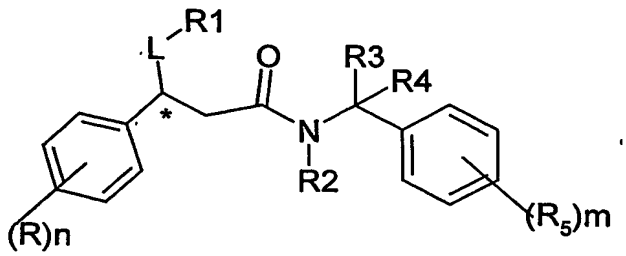
i) removal of any protecting group;

ii) isolation of the compound as a salt or a solvate thereof;

iii) separation of a compound of formula(I) or derivative thereof into the enantiomers thereof.

Abstract

The present invention relates to heterocyclic derivatives of formula (I)



(I)

wherein

R represents halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl or trifluoromethoxy;

R_1 represents a 5 or 6 membered heteroaryl group, in which the 5-membered heteroaryl group contains at least one heteroatom selected from oxygen, sulphur or nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms, or R_1 represents a 4, 5 or 6 membered heterocyclic group, wherein saids 5 or 6 membered heteroaryl or the 4, 5 or 6 membered heterocyclic group may optionally be substituted by one to four substituents, which may be the same or different, selected from $(CH_2)_pR_6$, wherein p is zero or an integer from 1 to 4 and R_6 is selected from:

halogen,
C_{1-4}alkoxy,
C_{1-4}alkyl,
C_{3-7}cycloalkyl,
hydroxy,
cyano,
nitro,
trifluoromethyl,
carboxy,
$NH(C_{1-4}$ alkyl),
$N(C_{1-4}$ alkyl$)_2$
$NH(C_{3-7}$ cycloalkyl),
$N(C_{1-4}$ alkyl$)(C_{3-7}$ cycloalkyl);

provided that saids 5 or 6 membered heteroaryl or 4, 5 or 6 membered heterocyclic are linked to the carbon atom shown as * via a carbon atom;

R_2 represents hydrogen, or C_{1-4} alkyl ;

R_3 and R_4 independently represent hydrogen, C_{1-4} alkyl or R_3 together with R_4 represents C_{3-7} cycloalkyl;

R_5 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

L is a single or a double bond;

n is an integer from 1 to 3;

m is zero or an integer from 1 to 3;
and pharmaceutically acceptable salts and solvates thereof, process for their preparation and their use in the treatment of condition mediated by tachykinins and/or by selective inhibition of serotonin reuptake transporter protein.